Pleural Effusion Prediction Failures

Correctly categorizing pleural fluid of uncertain etiology as an exudate increases clinical diligence to seek the cause of the effusion from a concerning list of inflammatory and malignant conditions. The ability to separate transudative from exudative pleural effusions by chemical analysis has gone through a gradual, historical evolution. Initially, specific gravity and absence or presence of clotting were used to try to distinguish these two types of pleural effusions. Later, a protein in the fluid greater than three g/dL or a high lactate dehydrogenase (LDH) level was utilized to diagnose an exudative process. In the classic article by Light et al,1 the presence of one or more of a combination of test results (pleural fluid-to-serum protein ratio > 0.5, pleural fluid LDH > 200 IU, and a pleural fluid-to-serum LDH ratio > 0.6) diagnosed an exudate. Light’s criteria continue to be the most widely accepted method to distinguish pleural fluid transudate from exudate. A variety of other tests (cholesterol, albumin, and bilirubin) have been tested to try and improve accuracy on Light’s criteria and on clinical impressions.2–4 No single test or cluster of tests, even when combined with clinical circumstances, have been sufficient to absolutely distinguish exudate from transudate.

Some tests of pleural fluid do have diagnostic absoluteness. For example, finding malignant cells in pleural fluid confirms a malignant effusion. Finding bacteria, tuberculosis, or fungi confirms an empyema, tuberculous effusion, or fungal-infected effusion, respectively. Finding an extremely low pH and increased amylase in the face of known esophageal injury confirms an esophageal rupture as cause for the pleural fluid. No definitive diagnosis is made using any of the tests that distinguish transudate from exudate. None of the specific diagnoses made from pleural fluid analysis utilize protein, LDH, albumin, or any of their ratios or gradients.

In this issue of CHEST (see page 1524), Romero-Candela et al tried to utilize biochemical criteria in addition to clinical judgment to separate transudate from exudate. Two hundred forty-nine patients had diagnostic thoracentesis, and two physicians clinically classified the effusions as transudate or exudate before the thoracentesis. The preprocedure clinical impression of transudate or exudate was changed 38 times (15%). Although the change in classification of the fluid by clinical status did not influence the overall accuracy, the changes made by the clinicians demonstrate how difficult it can be to determine the etiology of many effusions based alone on clinical data. In addition, 17 patients were excluded because the cause of the effusion was “indeterminate.” Establishing a “gold standard” definition of transudate and exudate to compare against any measured test or set of tests is clearly impaired when the initial clinical presumption as to the type of effusion changes 15% of the time and when 6% of the effusions are excluded as indeterminate. In establishing gold standards against which tests are measured, a conflict arises in using the measured test to set the standard.

Similarly, in Light’s classic article of the 150 patients with pleural fluid assessment, 33 patients (22%) were excluded because clinical criteria were insufficient alone to determine the cause of the effusion. Excluding patients with effusions of undetermined etiology dramatically changes the accuracy of any testing. Determining if pleural fluid is an
exudate or transudate is also made difficult when: (1) an assumption of etiologic dichotomy is made for the effusion analysis, (2) the fluid analyses are at the dichotomous cut-points between exudate and transudate, and (3) the clinician has no clear etiology for the effusion.

The article by Romero-Candeira et al confirms again the value of Light’s criteria as a screen for exudative pleural fluid with a sensitivity of 99.5%. This high sensitivity comes at a cost of high false-positive results. The accuracy of albumin gradient, protein gradient, and clinical presumptions was less than the accuracy of Light’s criteria alone. Both albumin and protein gradients had a nonstatistically significant increase in accuracy when classifying effusions in patients receiving diuretic therapy. The data from this study do not suggest changing the approach to patients with pleural effusions other than considering obtaining a protein gradient for those receiving diuretics. Theoretically, an albumin gradient would more accurately reflect changes in oncotic pressures more than total protein gradient, but the analysis of albumin and protein gradient in this study shows no clinically significant difference.

Determining the etiology of the effusion when multiple causes of pleural fluid exist remains problematic. In this study, 44 patients with congestive heart failure clinically had other suspected causes of the effusion that justified thoracentesis. Only 11 of the 44 patients had a lack of response to diuresis as the indication for thoracentesis. The effusion that is a transudate by laboratory analysis but contains malignant cells is often categorized based on the response to treatment or excluded from studies as indeterminate.

No single test or group of tests will likely distinguish transudate from exudate when the results are marginal and the clinical circumstances uncertain. An intriguing approach to this problem was outlined in a previous article in CHEST by Heffner et al (June 2002), who looked at multilevel likelihood ratios for identifying exudative pleural effusions. This intriguing concept suggests that the test alone does not distinguish exudate from transudate; rather, the test only influences the likelihood of being an exudate or transudate. Using the laboratory data from the effusion to determine a likelihood ratio that is then applied against pretest probabilities will marginally improve classification of the fluid when the pretest probability for either exudate or transudate is overwhelming. If the etiology of the effusion is not clear and the tests analyzing the effusion are marginally predictive, a significant insecurity as to the final classification will remain. With these most-difficult-to-categorize effusions, there is not perfect, predictive test.

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REFERENCES


Talc for Pleurodesis?

At the present time, talc is the agent for pleurodesis that is preferred by the majority of chest physicians in the United States and England. The reason for this preference is that talc, administered either by an aerosol (insufflation) or in a suspension (slurry), is effective, inexpensive, widely available, and associated with minimal side effects in most reports.

Concerns, however, remain about the safety of talc. The primary worry is the observation that ARDS can develop after its intrapleural administration. There are at least 42 cases of ARDS following intrapleural talc administration in the literature, 24 following the use of talc slurry and the remaining 18 following talc insufflation.1–10 In some cases, the patients presented with respiratory failure and were on mechanical ventilation. Eleven of the patients died.1,4,6,8–10 The reports of this complication seem to be increasing recently. In one recent article from New Zealand, Brant and Eaton10 reviewed their experience with 33 pleurodesis procedures in 29 patients. They reported that major complications (ie, hypoxemia and hypotension) occurred in seven patients and that two of the patients died.10 In